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Direct Invasion of the Optic Nerves, Chiasm, and Tracts by *Cryptococcus neoformans* in an Immunocompetent Host

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Abstract

Cryptococcus spp is a common fungal infection and frequent cause of meningitis in immunocompromised patients; however, immunocompetent patients are also at risk of infection. Visual loss often occurs via elevated intracranial hypertension but can rarely occur through direct optic nerve, chiasm, or tract invasion. We report a case of a 38-year-old woman who presented with decreased acuity in both eyes. She had generalized visual field constriction in the right eye and temporal hemianopsia in the left eye. Magnetic resonance imaging of the brain and orbits showed multiple areas of ill-defined enhancement in the optic chiasm and tracts as well as in the diaphragmatic sella, prepontine and interpeduncular cisterns, and along cranial nerves VI, VII, and VIII bilaterally. Initial cerebrospinal fluid (CSF) showed 34 white blood cells, hypoglycorrhachia, and negative cryptococcal antigen and bacterial and fungal cultures. A transphenoidal biopsy of the dura and pituitary gland was unremarkable. Empiric steroids resulted in marked improvement in visual acuity in both eyes, but while tapering steroids, she developed rapid visual loss bilaterally. Repeat CSF performed 6 weeks later demonstrated a cryptococcal antigen titer of 1:512. Retroactive staining of the pituitary biopsy was positive for mucicarmine, a component of the polysaccharide capsule of *Cryptococcus* spp. After induction therapy with amphotericin B and flucytosine and 1 year of fluconazole, her visual acuity was 20/20 in both eyes. In summary, *Cryptococcus* can affect immunocompetent patients and often presents with insidious, chronic meningitis. Visual loss is common in cryptococcal meningitis but usually results from fulminant papilledema related to elevated intracranial pressure. In rare cases, direct nerve or chiasm infiltration by the fungus results in vision loss.

Keywords

central nervous system fungal infections, central nervous system infections, meningitis, infectious disease medicine, neuroophthalmology, cryptococcus

Case Report

A 38-year-old woman with no past medical history presented with difficulty reading in April. Her vision gradually declined and by September her visual acuity was 20/200 in the right eye, 20/50 in the left eye and she had dyschromatopsia in both eyes and bilateral optic disc pallor. In addition, her Humphrey 24-2 visual fields showed generalized visual field constriction in the right eye and temporal hemianopsia in the left eye, suggesting involvement of the chiasm and right optic nerve. The rest of her general and neurological examination was normal including the remainder of her cranial nerves. An magnetic resonance of imaging (MRI) of the brain and orbits showed multiple areas of ill-defined enhancement in the optic chiasm and tracts as well as the diaphragmatic sella, prepontine and interpeduncular cisterns, and along cranial nerves VI, VII, and VIII bilaterally.

She was referred to our institution's neurology department in November when she noted progressive difficulty preparing her lesson plans and driving at night. Her examination was remarkable for visual acuity, 20/400 in the right eye and

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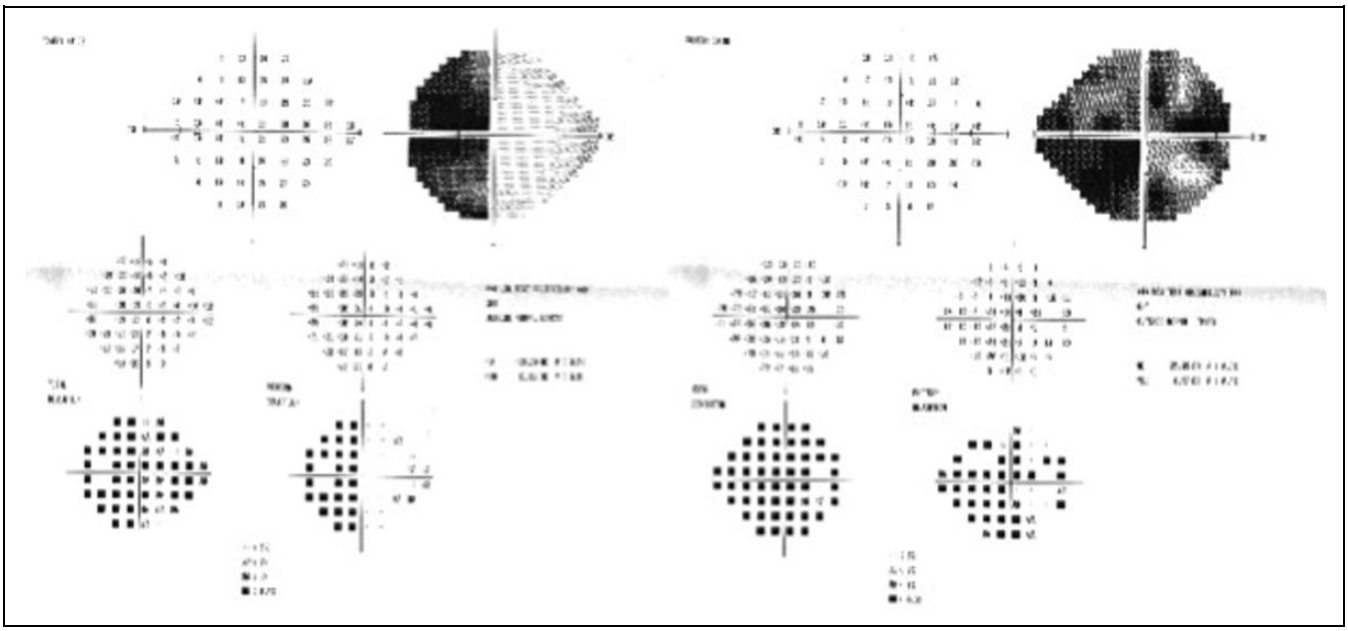

Figure 1. Humphrey Visual Fields. Humphrey Visual Fields show an incongruous left homonymous hemianopia with an additional superior arcuate defect in the right eye.

20/50 in the left eye with a right relative afferent pupillary defect. There was an incongruous left homonymous hemianopia with an additional superior arcuate defect in the right eye on Humphrey 24-2 visual field testing (Figure 1). Repeat MRI of the brain (Figure 2) showed similar findings of diffuse nodular ill-defined leptomeningeal enhancement. In addition, an MRI of her spine showed patchy leptomeningeal enhancement.

A lumbar puncture (LP) was performed on November 16 with cerebrospinal fluid (CSF) analysis showing 34 white blood cells, glucose <10 mg/dL, and protein 231 mg/dL and positive oligoclonal bands with negative cryptococcal antigen, cytology, and cultures including Gram stain, bacterial and fungal cultures, acid-fast stain, lyme antibody, and Venereal Disease Research Laboratory test (Table 1). Laboratory studies were unremarkable, including complete metabolic panel, complete blood count, HIV enzyme-linked immunosorbent assay, Quantiferon gold, erythrocyte sedimentation rate, C-reactive protein, lyme serologies, angiotensin-converting enzyme, double stranded DNA, and Anti-Sjögren's-syndrome-related antigens A & B. An ANA was positive at 1:40. A computed tomography scan of her chest, abdomen, and pelvis was unremarkable as was a whole-body positron emission tomography scan and bone marrow biopsy. A repeat LP performed 5 days later was again unremarkable (Table 1).

Her symptoms persisted and a transphenoidal biopsy of the leptomeninges in the region of the pituitary gland was performed but was unrevealing. Intraoperatively, the pituitary gland was debulked, perhaps leading to significant decompression of the optic chiasm as immediately postoperatively her symptoms significantly improved. Her neurological examination was normal with full visual fields and improved visual acuity, that is, 20/30 bilaterally. Neurosarcoidosis was considered the most likely diagnosis, and empiric prednisone 60 mg daily was initiated on discharge.

Seven days later, while tapering corticosteroids, she returned with complaints of rapidly progressive vision loss. Her visual acuity was light perception in the rigth eye and 20/400 in the left eye. A repeat MRI demonstrated continued multifocal leptomeningeal enhancement as well as increased ventricular size suggestive of moderate hydrocephalus. A repeat LP was performed on December 27. The opening pressure was 31 mm Hg and the CSF (Table 1) was positive for cryptococcal antigen (titer 1:512) with Gram stain showing multiple budding yeast forms and many white blood cells (Figure 3). *Cryptococcus neoformans* var. *grubii* was grown in the culture. Antifungal treatment was initiated and included intravenous amphotericin and flucytosine for 4 weeks followed by oral fluconazole for 1 year after the onset of her symptoms. Cerebrospinal fluid cultures at 2 and 4 weeks after the initiation of antifungal treatment were negative for viable *Cryptococcus* spp, and the CSF cryptococcal antigen titer decreased to 1:8. She was discharged home on daily fluconazole and a corticosteroid taper.

To determine whether cryptococcal meningitis was the underlining explanation for her disease manifestations versus whether it was a complication from immunosuppressive therapy, retroactive staining of the pituitary biopsy was performed with mucicarmine to identify the polysaccharide capsule of cryptococcal organisms (Figure 3). Although no definitive yeast forms were seen on the biopsy, the macrophages were positive for mucicarmine staining in the cytoplasm, suggesting that the yeast was present in the tissue prior to the initiation of corticosteroids. A repeat HIV enzyme immunoassay (EIA) and HIV viral load testing were also negative. To further investigate the patient's immune status, a T-cell lymphocyte panel was drawn

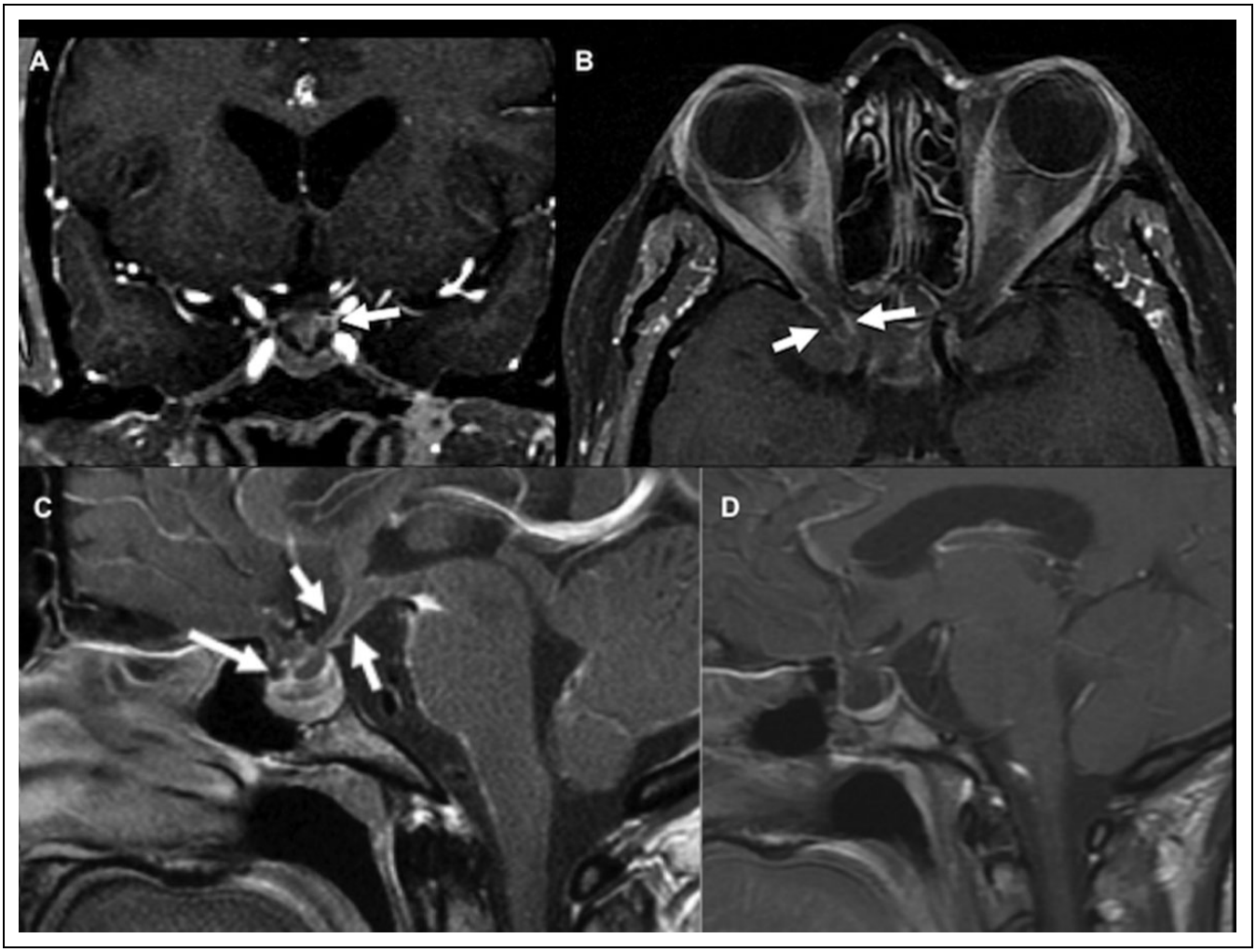

Figure 2. Magnetic resonance imaging (MRI) of the brain. Coronal T1W post-gadolinium image (A) from initial brain MRI demonstrates enhancement of the sella and the left optic nerve (arrow). Axial T1W post-gadolinium image (B) from initial brain MRI demonstrates leptomeningeal enhancement of the right optic nerve (arrows). Postgadolinium sagittal T1W sequence on initial MRI of the brain (C) demonstrates leptomeningeal enhancement around the sella, pituitary infundibulum, and prepontine cistern. After 1 year of antifungal treatment, sagittal postgadolinium T1W image (D) demonstrates resolution of the previously seen leptomeningeal enhancement around the sella, infundibulum, and prepontine cisterns.

and revealed a CD4 count of 283 mm^3 (normal range 387-1688 mm^3) and a CD8 count of 167 mm^3 (normal range 157-856 mm^3). The decreased CD4 count was attributed to ongoing corticosteroid use consistent with the decreased CD4–CD8 ratio.[1] After discontinuing corticosteroids, her CD4 and CD4 counts normalized to 946 and 714 mm^3, respectively.

On follow-up visit 1 year later, she was symptom free with visual acuity, 20/20 bilaterally. She continued to be maintained on fluconazole and prednisone. A repeat MRI of the brain was performed showing decreased leptomeningeal enhancement (Figure 2).

Discussion

We report a case of invasion of the optic apparatus by *Cryptococcus neoformans* in an immunocompetent patient. Cryptococcal infection likely caused her visual disturbances, which insidiously worsened, despite brief periods of improvement due to corticosteroids. Although her original CSF cryptococcal antigen test was negative, both culture and antigen were positive after 6 weeks of ongoing symptoms. The positive mucicarmine staining in the pituitary biopsy is highly suggestive of *Cryptococcus*.

Cryptococcosis is the most common systemic fungal infection in immunocompromised patients and a frequent cause of central nervous system infection. Immunocompetent patients are also at risk of infection; however, they often present with a more insidious form of meningitis than those patients who are immunocompromised.[2] Transmission occurs through inhalation of aerosolized spores resulting in an often subclinical pneumonitis.[3] Following hematogenous spread, chronic or subacute meningoencephalitis is the most common manifestation,

Table 1. Results of Cerebrospinal Fluid Analysis.

	First Admission		Fourth Admission			Outpatient	Fifth Admission	
Lumbar Puncture	1	2	3	4	5	6	7	8
Date	November 16	November 21	December 27	January 2	January 11	January 23	February 8	February16
OP (cm H_2O)	22	29	31	17	28	29	34	17
Color[a]	Clear	Clear	Clear	Clear	Clear	Clear[b]	Clear[c]	Clear
Appearance[a]	Colorless	Colorless	Colorless	Colorless	Colorless	Xanthochromic[b]	Colorless[c]	Colorless
Red cell count, per mm^{3a}	0	1	22	120	11	1600[b]	0[c]	1
White cell count, per mm^{3a}	34	58	54	43	22	6[b]	36[c]	8
Differential count, %[a]								
Neutrophils	26	57	54	1	74	8[b]	28[c]	2
Lymphocytes	59	41	42	78	19	90[b]	58[c]	81
Glucose (mg/dL)	<10	11	27	61	40	41	28	49
Protein (mg/dL)	231	195	80	56	54	61	153	52
Microbiology								
Gram stain	Few WBCs	Negative	Yeast, WBCs	Sparse yeast, sparse WBCs	Yeast, WBCs	WBCs	WBCs	WBCs
Culture	Negative	Negative	Few *Cryptococcus neoformans*	Not viable	Not viable	Negative	Negative	Negative
Fungus culture	Negative	Negative		Negative	Negative	Negative	Negative	Negative
Cryptococcal antigen, titer	Negative		Positive (1:512)	Positive (1:512)	Positive (1:8)	Positive (1:8)	Positive (1:1)	Positive (1:2)
Acid-fast bacteria culture	Negative	Negative						Negative
Lyme antibody	Negative							
Epstein Barr Virus quantatative polymerase chain reaction		Negative						
Venereal Disease Research Laboratory test	Nonreactive							
ACE (Ref 0.0-2.5 U/L)	0.6		1.0	1.2	0.9			0.7
B2M (Ref 1.1-2.4 mg/L)	1.2							
Oligoclonal banding	Positive							
NMO			Negative					

Abbreviations: OP, opening pressure WBC, white blood cell; ACE, angiotensin converting enzyme; B2M, beta-2-microglobulin; NMO, neuromyelitis optica immunoglobulin G antibody.
[a]Analysis from tube 4 unless otherwise specified.
[b]Analysis from tube 1.
[c]Analysis from tube 2.

typically characterized by headache, fever, malaise, and altered mental status over the course of several weeks.[3]

Immunocompromised patients tend to present with a more acute, fulminant pattern of disease with higher rates of fungemia, higher serum cryptococcal antigen titers, and a poor CSF inflammatory response.[2-4] On the other hand, immunocompetent patients often present with a more insidious process involving recurrent episodes of nonspecific symptoms including headache, nausea, and cranial nerve palsies.[3,4] Interestingly, immunocompetent patients are more likely to show clinical signs of neck stiffness and papilledema and develop complications including altered mental status, cranial nerve lesions, and visual deficits.[5] Immunocompromised transplant patients may also have an indolent course due to the patient's inability to mount an inflammatory response.[6] In addition, cryptococcal meningitis may be part of an immune reconstitution inflammatory syndrome that may present with a clinical deterioration or new presentation of cryptococcal disease following initiation of antiretroviral therapy.[7]

There are also clinical differences based on the species. *Cryptococcus neoformans* represents a global, primarily opportunistic infection while *Cryptococcus gattii* affects primarily immunocompetent hosts and, until recently, was thought to be generally encountered in tropical and subtropical regions.[3,8] However, in 2004, a well-publicized outbreak of *C gattii* and *C neoformans* var *grubii* occurred on Vancouver

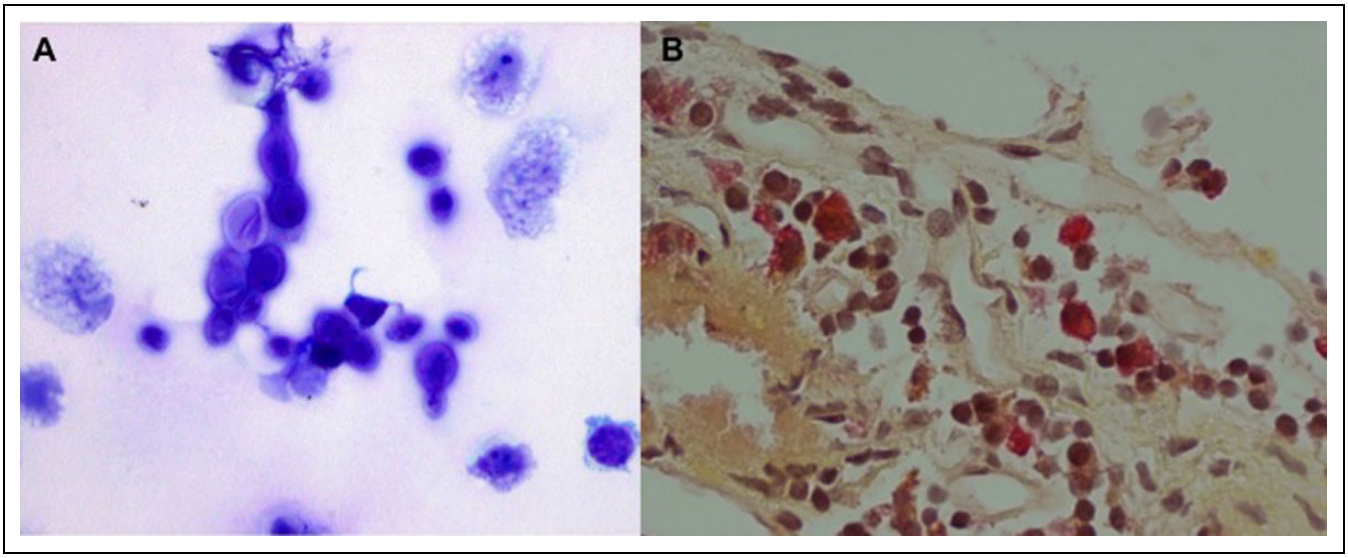

Figure 3. Cerebrospinal fluid Gram stain and pituitary biopsy. A, Gram stain of cerebrospinal fluid demonstrating budding yeast cells of *Cryptococcus* spp surrounded by white blood cells and (B) pituitary biopsy mucicarmine stain showing positive staining (in red) in macrophages indicating the presence of mucopolysaccharides. Color available in the online version of this article.

Island. In that outbreak, the majority of *C neoformans* cases affected HIV-positive patients, and *C gattii* affected HIV-negative patients.[9] In our case, an immunocompetent woman was affected by *C neoformans,* thus illustrating that infection with this subtype is not necessarily restricted to immunocompromised individuals.

Clinicians often face diagnostic uncertainty regarding the possibility of cryptococcosis in immunocompetent patients because of the nonspecific presentation, lower clinical suspicion, and decreased yield of diagnostic testing.[4,5,10] The sensitivity of CSF cultures to detect *Cryptococcus* spp ranges from 50% to 80%. The sensitivity of antigen detection is up to 96%.[11] The immune status of the patient may affect the yield of the test: in some studies, the sensitivity of CSF culture and cryptococcal antigen has been reported to be lower in immunocompetent patients, but in a more recent prospective study in Vietnam, all nonimmunocompromised patients had positive culture and antigen detection.[12] Immunocompetent patients therefore may be at a higher risk in obtaining a false-negative test and subsequently lead the clinician to a missed diagnosis.

Visual and ocular complications of cryptococcal meningitis are fairly common and occur more frequently in immunocompetent patients.[5] Complaints may include vision loss, ophthalmoplegia, papilledema, and optic atrophy.[13] Two patterns of visual loss have been proposed, namely, rapid and slow. Rapid visual loss occurs over hours and is often bilateral, severe, and permanent; optic neuritis is favored as the primary pathogenic mechanism.[8,14] In contrast, slow visual loss occurs over days, has a more favorable prognosis, and is thought to be secondary to the effects of intracranial hypertension and subarachnoid adhesions and occurs more commonly in immunocompetent patients.[8,14] Visual loss in our patient was unrelated to intracranial hypertension as there was never papilledema but instead appeared to result from a perineural and perichiasmal arachnoiditis. Prior reports have demonstrated infiltration of the optic nerves and tracts on autopsy and we suspect that this was the case in our patient.[15]

In conclusion, clinicians should be aware that *Cryptococcus* spp can affect immunocompetent patients and may present with insidious, chronic meningitis, and visual loss from infiltration or inflammation of the optic apparatus. Clinicians should consider cryptococcal meningitis as a possible diagnosis, despite initially negative tests such as CSF culture and cryptococcal antigen. In suspected cases, clinicians should have a low threshold to repeat these tests or perform a biopsy in order to diagnose and then treat this curable condition.

Declaration of Conflicting Interests

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